

**U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE**

REMARKS

A check for the fees for filing the RCE and for a three month extension of time accompanies this response. Any fees that may be due in connection with filing this paper or with this application during its entire pendency may be charged to Deposit Account No. **06-1050**. If a Petition for extension of time is required, this paper is to be considered such Petition, and any fee charged to Deposit Account No. **06-1050**.

Claims 23-60 are pending in the instant application. Applicant respectfully requests entry of the Amendment after Final filed March 23, 2004, responsive to the Final Office Action. Such request is indicated on the Request for filing the RCE.

THE REJECTION OF CLAIMS 23-60 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims **23-60** are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement, for reasons of record in previous Office Actions. In addition, in the Advisory Action mailed April 28, 2004, the Examiner states that the arguments and amendments filed responsive to the Final Office Action have been considered but allegedly do not place the application in condition for allowance. Referring to particular arguments made by Applicant in the Amendment after Final filed March 23, 2004, responsive to the Final Office Action, the Examiner sets forth rebuttals in the Advisory Action as follows:

(A) Applicant's argument that Claim 1 is outside the purview of the rejection because it is not directed to a method of making a transgenic animal is deemed not persuasive because "the intended use of the resultant cell of claim 1 is for producing a transgenic animal."

(B) Responsive to Applicant's alleged arguments that the case law cited by the Examiner is "not relevant," the Examiner rebuts that the case law is in fact relevant to the instant case because it relates to "unpredictable art," which allegedly is the issue at hand.

**U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE**

(C) Applicant's alleged argument that the disclosure of Wilmut *et al.* is presumptively enabled because a U.S. patent has issued is deemed unpersuasive because "the issue of enablement of Wilmut was raised based on the questions raised in the state of the art."

(D) Applicant's arguments that the method of Schnieke *et al.* follows the method of Wilmut *et al.* but for very minor modifications are deemed unpersuasive because "applicants do not provide any evidence except for arguments that examiner's enablement analysis was not correct."

This rejection is respectfully traversed. Each of the Examiner's rebuttals set forth in the Advisory Action are addressed in turn below. These rebuttals also are adequately addressed in the Amendment after Final filed March 23, 2004, responsive to the Final Office Action. Entry of the aforementioned Amendment after Final respectfully is requested herein.

Analysis

I. It is respectfully submitted that the rejection as set forth in the instant Advisory Action and in previous Office Actions confuses two grounds for rejection: (1) lack of enablement and (2) lack of utility cast as a rejection for lack of enablement. Applicant's previous responses to each of these issues (*i.e.*, lack of enablement and lack of utility under the guise of lack of enablement), including the Amendment after Final filed responsive to the Final Office Action, are summarized below and the issues are further addressed herein. Following the summary, Applicant has addressed each of the rebuttals (see **(A)** through **(D)** above) set forth in the Advisory Action.

II. In addition, and significantly, not all pending claims are within the purview of the rejection that the specification is not enabled for generation of a transgenic animal. For example, the independent claim, claim 23 is directed to:

A method, comprising:

introducing an artificial chromosome into a nuclear donor cell; and transferring the nucleus of the nuclear donor cell into an enucleated recipient cell.

**U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE**

Claim 23 does not require nor set forth generation of a transgenic animal, but only recites that the artificial chromosome is introduced into a nuclear donor cell whose nucleus is then transferred into an enucleated recipient cell. The operability of production of transgenic animals is not relevant to this claim. Similarly, claims 24, 25, 27-30, 32-39 and 41-56 are outside the purview of the rejection. The rejection that the claims are not enabled for the generation of transgenic animals is only pertinent to claims 26, 31, 40 and 57-60.

The Examiner asserts in the Advisory Action that the rejection is proper because the "intended" use of Claims 23, 24, 25, 27-30, 32-39 and 41-56 is for generation of a transgenic animal. As Applicant respectfully submits, however, in the section below rebutting the Examiner's assertions in the Advisory Action (see page 19), the Examiner provides no substantiation for the bald assertion that the only intended use of the claims is for generation of a transgenic animal. Moreover, the relevant question with regard to enablement of the subject matter of the instant claims is whether the particular steps and materials of the claimed methods are described in the specification in such a way as to enable one skilled in the art to make and use the subject matter **as claimed**, not as it is applied in a subsequent use.

(1) Lack of Enablement

(a) The specification provides an enabling disclosure for the claimed methods: no additional "evidence" is necessary

As discussed in the responses to previous Office Actions, including the Amendment after Final filed March 23, 2004, whose entry respectfully is requested herein, Applicant has demonstrated that the disclosure is enabling by providing a detailed analysis of the factors enumerated in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988); the analysis demonstrates that the amount of experimentation required to perform the claimed methods is not undue. Contrary to the Examiner's assertions, no additional evidence is required to support enablement of each of the steps of the claimed methods or the methods

U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE

as a whole because of the breadth of the claims (see, *e.g.*, claim 23) the teachings of the specification, the working examples, the advanced state of the art and knowledge of those of skill in the art, evidences that undue experimentation is not required to practice the methods as claimed.

In the Advisory Action, the Examiner, citing In re Scarbrough 182 USPQ (CCPA 1974), states that "argument alone cannot take the place of evidence lacking in the record." It is respectfully submitted that Applicant did not provide arguments to replace evidence lacking in the record. Rather, Applicant demonstrated that no additional evidence is required in support of an analysis that the specification as filed is enabling for the methods as claimed.

In In re Scarbrough, the Court held that there was information missing from the specification because it did not provide a disclosure of how components that had previously been used in other systems were related in Applicant's particular system, nor how to arrive at such relationship without undue experimentation. The instant specification, on the other hand, teaches exactly how to perform each step of the methods as claimed by Applicant, including (i) introducing artificial chromosomes into a variety of cells; (ii) transferring a non-human mammalian donor cell nucleus into an enucleated acceptor cell of the same species; and (iii) generating a non-human mammalian transgenic animal from the resulting acceptor cell.

For example, as discussed in great detail previously, the specification describes (page 11, lines 14-18 *e.g.*) how to introduce artificial chromosomes into cells for various uses, by using microinjection, cell fusion, microcell fusion, electroporation, electrofusion, projectile bombardment, nuclear transfer, calcium phosphate precipitation, lipid-mediated transfer systems and other such methods. These methods, in light of the state of the art as of filing and the knowledge of those of skill in the art as evidenced by numerous publications incorporated by reference in the application, are applicable to the introduction of artificial chromosomes into a variety of cells and nuclei from different species.

U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE

The specification also teaches in great detail and provides working examples (Example 1 beginning at page 69, Example 13 beginning at page 165) demonstrating techniques such as microinjection, microcell fusion and cell fusion to introduce artificial chromosomes into cells and to further introduce the resulting donor cells into recipient acceptor cells.

The specification also describes and incorporates by reference Wilmut *et al.* (1997) Nature 385:810-813, International PCT application Nos. WO 97/07669 and WO 97/07668). The specification exemplifies the steps of the methods as instantly claimed in which an artificial chromosome is introduced by any suitable method into an appropriate donor cell, such as a mammary gland cell, is then introduced, such as by cell fusion or microinjection, into an unactivated oocyte, preferably enucleated cell. The specification provides how enucleation may be effected, how the recipient oocyte is activated, and how to produce a reconstituted mammalian embryo, which is then introduced into a mammalian host. The state of the art of nuclear transfer was advanced at the time the instant application was filed, the steps as described herein being applied to many mammalian species. Applicant has, moreover, provided working examples showing that artificial chromosomes encoding genes can be introduced into cells, stably expressed therein, fused with suitable recipient cells, and used to generate transgenic animals (see, e.g., Example 13, at page 165 of the specification, which describes methods for the microinjection of artificial chromosomes into eukaryotic cells, and detection of expression of the encoded heterologous DNA (β Gal) in cells injected with the DNA. Example 14, at page 168 of the specification, describes in great detail the development of transgenic mice expressing the anti-HIV ribozyme encoded by an artificial megachromosome. Example 14 also describes in great detail the uses of the artificial chromosomes in generating transgenic animals).

Therefore, contrary to the Examiner's assertions, there is no evidence "lacking" in the record. Unlike In re Scarbrough, where the disclosure failed to

U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE

provide how the claimed system was assembled as a series of inter-related components, the instant application teaches and provides working examples of nuclear transfer methods and the generation of transgenic animals therefrom as instantly claimed, *i.e.*, by teaching how to (i) introduce artificial chromosomes into a variety of cells, including those that can be used as donor cells for nuclear transfer; (ii) transfer a non-human mammalian donor cell nucleus into a recipient acceptor cell; and (iii) generate a non-human mammalian transgenic animal from the resulting acceptor cell.

The Examiner appears to be alleging that the information "lacking" in the record is a teaching in the specification of how to adapt the disclosed method to different cell types from different species. The Examiner points to the alleged "unpredictability" of nuclear transfer as the basis for this allegation, and in previous Office Actions has cited several post-filing references in support of this assertion. As discussed below, however, the specification, in light of the knowledge of those of skill in the art, teaches a method of nuclear transfer that requires at most routine experimentation in order to be applicable to a variety of mammalian species. Further, Applicant has provided evidence showing the state of the art of nuclear transfer at the time the instant application was filed, was sufficient to render the method predictably applicable to a variety of mammalian species.

(b) Notwithstanding the fact that there is no evidence lacking in the record, Applicant has provided additional evidence in the form of references demonstrating that the art of nuclear transfer at the time of filing and as of its earliest priority date was broadly and "predictably" applicable to a variety of mammalian species.

In the instant Advisory Action and in previous Office Actions, the Examiner cites a single factor, "unpredictability," as the basis for alleging lack of enablement of the generation of transgenic animals by nuclear transfer. The Examiner has previously cited several post-filing date references in support of this allegation, including: Stice *et al.* (*Theriogenology* 49:129-138, (1998));

U.S.S.N. 09/836,911
HADLACZKY et al.
RESPONSE AND RCE

Yanagimachi (*Mol. Cell. Endocrin.* 187:241-248 (2002)); Oback and Wells (*Cloning and Stem Cells*, 4:169-174, (2002)); and Kuhholzer and Prather (*Soc. Exp. Biol. Med.*, 224:240-245, (2000)). Post-filing date references can potentially be used to establish inoperativeness (no such rejection has been set forth in the prosecution history of this case). A rejection for lack of enablement derives from the fact that one cannot teach how to make and use something inoperative. This reasoning has not been set forth (nor is appropriate since the instantly claimed methods are operative). If the Examiner sets forth such grounds, then any Action containing such rejection cannot properly be made final.

The Examiner also cites Co *et al.* (*Chromosome Res.*, 8:183-191, (2000)) as a reference that concededly shows that SATACS introduced into mouse embryos by pronuclear microinjection are stable, but then goes on to assert that although this article teaches that the SATACS are stable, the introduction of a SATAC containing a heterologous sequence in a donor cell and use of the donor cell in producing a transgenic mammal "will be unpredictable" in view of the discussion above.

First, as discussed previously, Applicant maintains that, regardless of whether the Examiner considers an alleged "unpredictability" of the instant claimed methods to provide "reasonable doubt" of the disclosure being enabling (*Ex parte Singh*), the inquiry with respect to enablement under 35 U.S.C. §112, first paragraph, is whether it would require *undue experimentation* to make and use the claimed subject matter. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). A consideration of whether or not undue experimentation is required takes into account a number of factors, of which predictability is only one factor. Further, it is inapt to cite post filing-date references to establish a lack of enablement of the specification as of its priority date.

U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE

Applicant, on the contrary, has provided a detailed analysis under In re Wands, demonstrating that the specification meets the standard for enablement. In addition, Applicant has provided evidence in the form of numerous references demonstrating that, at prior to the effective filing date of the claims at issue, nuclear transfer was known and had successfully been applied to a variety of mammalian species.

The Examiner is reminded that evidence demonstrating enablement can be provided in the form of cited references to show what one of skill in the art knew at the time of filing the application (MPEP 2164.05). It is respectfully submitted that the Examiner has failed to consider the various references (*see, e.g.*, Wells *et al.*, *Biol. Reprod.*, 57:385-393 (1997); Campbell *et al.* (1996) *Nature* 380:64-66; PCT Application Publication No. WO95/17500; Solter (1996) *Nature*, 380: 24-25; Sims *et al.* (1993), *Proc. Natl. Acad. Sci. USA*, 90:6143-6147) provided by Applicant that demonstrate the advanced state of the art of nuclear transfer methods and the production of transgenic animals such as bovines, ovines and ungulates therefrom as of the instant claims' effective filing date. Further, even Wolf *et al.*, cited by the Examiner as allegedly demonstrating that the method of Wilmut *et al.* is inoperative, discusses how nuclear transfer has successfully been carried out since the early 1980's and prior to the instant application's earliest priority date in such diverse mammalian species as sheep, goats, cattle, rabbits, pigs, mice and monkeys (*see pp.99-100*).

A method can be deemed "unpredictable" if one of skill in the art could not "readily anticipate the effect of a change within the subject matter" at the time the application was filed (MPEP 2164.04) or the method is "contrary to generally accepted scientific principles." (In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971). All of the above cited references describe practice the method of nuclear transfer as taught in the specification, namely, isolating and culturing suitable mammalian nuclear donor

U.S.S.N. 09/836,911

**HADLACZKY *et al.*
RESPONSE AND RCE**

cells, passaging the cells, if needed transfecting the cells with a transgene of interest, fusing the cells with enucleated mammalian acceptor cells of the same species, and allowing the resulting acceptor cell to develop into a transgenic animal. Further, all the cited references describe the successful generation of a transgenic animal. Therefore, there is no dramatically different or contrary or "unpredictable" result when the methods of nuclear transfer in the state of the art are applied to different species. As discussed previously, Applicant is not aware of any requirement under current U.S. patent law specifying particular minimum levels of optimization and certified efficacy in order for an area of art to qualify as sufficiently "predictable" such that lack of enablement under 35 U.S.C. § 112, first paragraph, is not a consideration. The relevant standard is not that of an established, fully optimized, method; rather, a patent application satisfies the requirements of 35 U.S.C. § 112, first paragraph, as long as it provides sufficient disclosure, either through illustrative examples or terminology, to teach those of skill how to make and use the claimed subject matter with reasonable, but not undue, experimentation. Therefore, given the claims at issue, the state of the art of conducting nuclear transfer in a variety of mammalian species as of the instant application's filing date, and the evidence provided by Applicant in support thereof, it is respectfully submitted that, in light of the teachings of the specification and the knowledge of those of skill in the art as of the application's earliest priority date, the method of nuclear transfer can "predictably" be applied to any desired mammalian species.

Furthermore, as discussed in responses to previous Office Actions and herein, regardless of the inapt citation of post-filing date references to establish lack of enablement, the Examiner's cited references provide no evidence of "unpredictability" of the instantly claimed methods. As discussed in previous responses, none of the references cited by the Examiner deviate from the method of nuclear transfer taught in the specification, but for species-based variations in parameters such as efficiency, donor cell selection, and cell cycle

U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE

synchronization. It is respectfully submitted that such experimental variation is not undue because, as evidenced by scores of publications since the early 1980's to the time the instant application was filed, some of which are of record in the file history of the instant application, these are standard parameters subject to routine experimentation in the art of nuclear transfer. The Examiner is reminded that even complex experimentation is not necessarily undue if the art typically engages in such experimentation (Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985)). None of the parameters varied in the references cited by the Examiner are ones whose variability would not readily and predictably be expected when the art of nuclear transfer is applied to a different species.

None of the references cited by the Examiner describes contrary or "unpredictable" results. All acknowledge that the overall efficiency of nuclear transfer can be low, but that its promise is nonetheless great and its applicability to a wide variety of species certain. In fact, one of the cited references, Stice *et al.*, goes so far as to speak of the commercial applicability of nuclear transfer, discussing how the commercial use of nuclear transfer is not limited by inefficiencies in nuclear transfer procedures, because only a few cloned transgenic founder animals are needed (see, e.g., page 133, "Commercial Applications of Cloning").

The Co *et al.* (*Chromosome Res.*, 8:183-191, (2000)) reference cited by the Examiner, in addition to being an inapt citation of a post-filing date reference to establish lack of enablement, does not in any way address "predictability" of the methods as instantly claimed. It is respectfully submitted that the Examiner's reliance upon Co *et al.* is speculation that if, instead of the disclosed methods of pronuclear microinjection therein, they carry out a method of nuclear transfer using the artificial chromosome - containing donor cells, the use of the donor cell to produce a transgenic animal "will be unpredictable" (emphasis added), does not establish any lack of enablement of the methods of nuclear

U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE

transfer as instantly claimed. To the contrary, Co *et al.* teaches that satellite DNA-based artificial chromosomes (SATACS) can be successfully delivered to (by pronuclear microinjection) and stably maintained and expressed in transgenic animals, with few inter-species differences (murine vs. bovine, *see, e.g.*, pp. 183-184), thus evidencing the desirability of using artificial chromosomes in methods for the generation of transgenic animals.

Moreover, as discussed below, by citing post-filing date references and alleging that the claimed methods are not "reproducible," the Examiner is in fact alleging that the claimed methods are not operative *i.e.*, they do not work. Such an assertion should properly be made under 35 U.S.C. § 101 on the grounds of lack of utility. As discussed below and previously, Applicant has responded to the allegations of lack of operability by showing that the methods taught in the specification are operative.

(2) Lack of Utility

(a) Post-filing date references are appropriately cited as evidence of inoperability or lack of utility under 35 U.S.C. § 101

In the reasons of record in previous Office Actions, the Examiner alleges that the method of Wilmut *et al.*, described in the disclosure and incorporated by reference therein, does not provide an enabling disclosure because this method allegedly has not been reproducible in other laboratories (citing Wolf *et al.*, *J. Biotechnol.*, 65:99-110 (1998)). Applicant respectfully submits that in making this statement, the Examiner is asserting a lack of utility of the method of nuclear transfer as taught in the specification because the method allegedly is "inoperative." The remaining post-filing date references cited by the Examiner and discussed above under "lack of enablement" also go to an allegation of lack of operability and may properly be applied in a rejection on grounds of lack of utility under 35 U.S.C. § 101.

(b) Wolf *et al.*, cited by the Examiner as evidencing irreproducibility of the method of Wilmut *et al.*, fails to demonstrate inoperability of the method.

U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE

The Examiner alleges that the article of Wilmut *et al.* does not provide an enabling disclosure because this method has not been reproducible in other laboratories (Wolf *et al.*, *J. Biotech.*, 65:99-110, (1998), page 101, first full paragraph in the right column). However, as discussed previously and herein, the passage from Wolf *et al.* cited by the Examiner as establishing that the method has not been reproducible in other laboratories, merely mentions that the result in Wilmut *et al.* of producing "Dolly", an animal cloned by nuclear transfer from an adult cell, had not been reproduced as of that date and had been questioned. Wolf *et al.* provides no evidence that the method of Wilmut *et al.* is inoperative. In fact, Wolf *et al.* describes how Wilmut *et al.* does demonstrate the use of fetal fibroblast cell lines in nuclear transfer experiments, resulting in live lambs (pg. 101, col. 2). Wolf *et al.* merely states that the result of obtaining a live lamb by nuclear transfer using an adult donor cell (*i.e.*, one embodiment of the method of Wilmut *et al.*), had been questioned.

A test for inoperability under 35 U.S.C. § 101 is whether the claimed subject matter is successful in achieving a useful result. "Partial success" is sufficient to demonstrate operability and utility; it is not essential that the claimed subject matter accomplish all its intended functions or operate under all conditions (In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995); In re Marzocchi, 439 F.2d 220, 169 USPQ 367 (CCPA 1971)). Thus, Wolf *et al.*, cited by the Examiner as evidence that the method of Wilmut *et al.* does not work, in fact acknowledges that Wilmut *et al.* works when fetal donor cells are used, and merely questions whether the method does work when adult donor cells are used. Therefore, even if Wolf *et al.* is correct in its assertion that the operability of the method of Wilmut *et al.* when adult nuclear donor cells are used is doubtful, the assertion, which does not challenge all embodiments of the method of Wilmut *et al.*, does not rise to the level of demonstrating inoperability.

U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE

Moreover, notwithstanding the above, Wolf *et al.* in fact does not establish that the method of Wilmut *et al.* does not work when adult nuclear donor cells are used. As discussed previously, Wolf *et al.* merely cites Sgamarella *et al.* (*Science*, 279(51):635-636, (1998); of record) and provides no disclosure as to whether the steps of the method, as actually practiced by one of skill in the art, would involve undue experimentation or be inoperable. As discussed below, Sgamarella *et al.* also does not establish that the method of Wilmut *et al.* does not work when adult nuclear donor cells are used.

A review of Sgamarella *et al.* indicates that this reference is critical of the success of Wilmut *et al.*, but again provides no evidence demonstrating that the disclosure of Wilmut *et al.* is not enabling or operative. Again, Sgamarella *et al.*, like Wolf *et al.*, only questions one embodiment of Wilmut *et al.*, namely, whether the method of Wilmut *et al.* works when adult nuclear donor cells are used. Sgamarella *et al.*, without providing any experimental evidence, only is skeptical of the reproducibility of the method of Wilmut *et al.* because Wilmut allegedly announced that he had no intention of practicing the method using adult donor cells, and because there "could have been" a stem cell in the adult mammary glad cell culture that was used in those experiments. Sgamarella *et al.* further expresses skepticism because a subsequent publication of Wilmut used a fetal cell rather than an adult cell in a nuclear transfer method, leading Sgamarella *et al.* to question whether Wilmut *et al.* used an adult cell and, if so, why "Dolly's" mitochondrial DNA was not analyzed to establish the same.

Neither an alleged decision by Wilmut not to practice the method of Wilmut *et al.* again, nor any of the allegations in Sgamarella *et al.* provide any evidence that the disclosure in Wilmut *et al.* is not enabling. Moreover, in a paragraph immediately following the article by Sgamarella *et al.*, Wilmut convincingly responded to Sgamarella's skepticism by stating that it is "highly inconceivable" that in the very short culture time of the adult mammary culture, a rare fetal cell could have multiplied so fast as to have overgrown the mammry

U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE

culture. Thus, even the single embodiment of the method of Wilmut *et al.* that is questioned by Wolf *et al.* and Sgamarella *et al.* as being suspicious, has not been substantiated by any actual demonstrations of inoperability.

(c) The remaining post-filing date references, including Co *et al.*, fail to establish inoperability of the claimed methods

Similarly, the remaining post-filing date references discussed above under "lack of enablement" due to alleged "unpredictability" of the claimed methods, in fact show that nuclear transfer methods are operative for a wide variety of species. Each demonstrates the generation of transgenic animals; therefore, each shows that method performs a "beneficial function" that meets the standard for operability.

With respect to Co *et al.*, cited by the Examiner as indicative of the lack of "predictability" of nuclear transfer using artificial chromosome-containing donor cells, as discussed previously, this assertion is mere speculation. Co *et al.* teaches that satellite DNA-based artificial chromosomes (SATAKS) can be successfully delivered by pronuclear microinjection and stably maintained and expressed in transgenic animals, with few inter-species differences (murine *vs.* bovine, *see, e.g.*, pp. 183-184). Co *et al.*, if anything, demonstrates the promise of artificial chromosomes as vectors to generate transgenic animals. Co *et al.* provides no disclosure of any nuclear transfer method, much less one that is "unpredictable" or "inoperative."

(d) The speculations and skepticism of the Wolf *et al.* and Sgamarella *et al.* references, and the Examiner's own speculation that the Co *et al.* method "will be unpredictable" when applied to nuclear transfer, are insufficient to establish lack of enablement of the instantly claimed methods or lack of a credible utility.

The USPTO has released "Guidelines for Examination of Applications for Compliance with the Utility Requirement" [guidelines, which address utility under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph] and an "Overview of Legal Precedent Governing the Utility Requirement" [legal overview] to

U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE

support the guidelines. Under section I.B.4. of these guidelines Examiners are reminded that:

they must treat as true credible statements made by an applicant or a declarant in the specification or in a declaration provided under 37 CFR §1.132, unless they can show that one of ordinary skill in the art would have a rational basis to doubt the truth of such statements. (emphasis added)

Further, the legal overview provided by the USPTO, in section II.B.1., explains that:

[a]n applicant's assertion of utility creates a presumption of utility that will be sufficient, in most cases to satisfy the utility requirement of 35 U.S.C. §101. To overcome this presumption, *the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility*. In other words, the Examiner must show that the asserted utility is not credible. [Emphasis added; see e.g., *In re Langer* 503 F. 2d 1380, 183 USPQ 288 (CCPA 1974)].

The legal overview goes on to explain, in section II.B.2., when an asserted utility is not "credible":

To assess credibility, the Examiner should determine if one of ordinary skill in the art would consider the assertions of the applicant to have any reasonable scientific basis. If they do, they should not be challenged as not being credible. Only where they do not [e.g., if the assertion is "incredible in view of contemporary knowledge"], should the Examiner challenge the statement as not being credible.

It is respectfully submitted that the speculative nature of Wolf *et al.* (citing Sgamarella *et al.*) and Co *et al.* as bases for rejections on the grounds of irreproducibility and unpredictability set forth by the Examiner fail to provide a rational basis or evidence that the method of Wilmut *et al.* and of the methods disclosed herein do not have credible utility.

Further, even if the Examiner (inappropriately) asserts that the Wolf *et al.* and Co *et al.* references are cited as evidence of the "unpredictable" state of the art at the time of filing, when rejecting a claim under the enablement requirement of 35 U.S.C. §112, "the PTO bears an initial burden of setting forth

**U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE**

a reasonable explanation as to why it believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The nature of this burden is further elucidated in In re Marzocchi (439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971)): "[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to *back up assertions of its own with acceptable evidence or reasoning* which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure" (emphasis added). It is respectfully submitted that speculation or skepticism is insufficient evidence and inadequate reasoning to challenge enablement of a disclosure.

(e) Applicant has provided ample evidence, including an issued patent with claims to the method of Wilmut *et al.* and the disclosure of whose parent application is incorporated by reference in the instant application, demonstrating that the claimed methods, including the method of Wilmut *et al.* described and incorporated by reference in the application, are operative.

As discussed previously, to evidence that the methods as claimed operate as claimed, Applicant provided publications (Schnieke *et al.*, *Science*, 278:2130-2133, (1997); WO 02/062131) demonstrating that by following the teachings of the application and that of Wilmut *et al.* incorporated therein, nuclear transfer and the generation of transgenic animals is obtained as claimed.

Also, as discussed previously, although these publications rebut assertions of inoperativeness, they also further evidence enablement. It is noted that the level of skill in the biotechnical arts is recognized to be high (see, e.g.,

U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE

Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'l 1986). Further, as discussed below, methods for performing the various steps of the claimed methods, such as introducing nucleic acids including chromosomes into nuclear donor cells, transferring the nuclei of the nuclear donor cells into recipient cells and allowing the recipient cell to develop into a transgenic fetus or animal in a host are known to the skilled artisan.

The reference Schnieke *et al.* demonstrates that by following the steps of nuclear transfer of Wilmut *et al.*, live transgenic sheep encoding human Factor IX were produced (*e.g.*, Table 1 at page 2131). The International Publication WO 02/062131 demonstrates that by following the steps of the method as taught in the instant specification (1) artificial chromosomes such as SATACS can be generated and introduced into nuclear donor cells; and (2) the nucleus of the nuclear donor cell can be transferred to into an enucleated recipient cell to yield bovine blastocysts. These blastocysts can then be placed in extended embryo culture and are capable of generating animals (bovines) (Examples 1-3, *e.g.*, beginning at page 55 of the specification).

Further, U.S. Patent No. 6,147,276, submitted by Applicant along with the previous response, is the issued patent whose disclosure is identical to that of PCT Application No. PCT/GB96/02099, published as WO 97/07669 and incorporated by reference in the instant application. Claims to the method of Wilmut *et al.* have issued in U.S. Patent No. 6,147,276, and these claims are presumptively enabled by the disclosure of U.S. Patent No. 6,147,276. Therefore, the disclosure of WO 97/07669, described and incorporated by reference in the instant application, which is identical to the disclosure in U.S. Patent No. 6,147,276, must be operative.

Furthermore, Wilmut *et al.*, published February 27, 1997, is a publication that is based on the disclosure of WO 97/07669. Because a U.S. Patent has issued with the same disclosure as WO 97/07669, and because a U.S. Patent is presumptively valid and enabled as of its filing date, the disclosure of WO

**U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE**

97/07669 described in the instant application and incorporated by reference is operative because claims that are based on the disclosure have issued in U.S. Patent No. 6,147,276.

Therefore, contrary to the Examiner's assertions regarding "non-reproducibility" of the method of nuclear transfer described in Wilmut *et al.*, it is respectfully submitted that Wilmut *et al.*, which is based on PCT Publication No. WO 97/07669, which in turn has the identical disclosure as that of U.S. Patent No. 6,147,276, is presumed to be operative and reproducible because the issued U.S. patent is presumptively valid (35 U.S.C. 282). Furthermore, the instant specification is reproducible and operative for the methods as claimed because it describes and incorporates by reference the methods of nuclear transfer provided in the International PCT Publication Nos. WO 97/07669 and Wilmut *et al.*.

**Rebuttal to specific issues raised in the Advisory Action responsive to
Applicant's previous response filed March 23, 2004**

(A) The Examiner alleges that Applicant's argument that Claim 1 is outside the purview of the rejection because it is not directed to a method of making a transgenic animal is deemed not persuasive because "the intended use of the resultant cell of claim 1 is for producing a transgenic animal."

First, it is respectfully pointed out that in the response filed March 23, 2004, Applicant inadvertently referred to Claims 23 and 24 as Claims 1 and 2. Applicant respectfully submits that the Examiner's assertion that the intended use is for generating a transgenic animal and no other purpose, is unsubstantiated. Although not limiting the claims to particular uses, Applicant respectfully submits that the claimed subject matter, including Claims 25, 27-30, 32-39 and 41-56 that are not directed to generating transgenic animals, can have other uses, such as in research.

Further, as discussed previously and herein, the relevant question with regard to enablement of the subject matter of the instant claims is whether the

U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE

particular steps and materials of the claimed methods are described in the specification in such a way as to enable one skilled in the art to make and use the subject matter **as claimed**, not as it is applied in a subsequent use. As recited, Claims 23 and 24 include the steps of introducing an artificial chromosome into a donor cell and then transferring the nucleus thereof into an enucleated recipient. Claim 24 further recites transferring the resulting recipient cell into a non-human maternal host animal. There is no requirement for generating a transgenic animal. Hence, Claim 23 and 24 are outside the purview of the rejection on the grounds that the specification is not enabling for the generation of a transgenic animal by nuclear transfer.

Furthermore, it is respectfully submitted that as discussed above, an analysis of the factors set forth in In re Wands, including the teachings of the specification, the working examples, and the advanced knowledge of those of skill in the art of nuclear transfer, leads to the conclusion that it would not require undue experimentation to make and use the claimed subject matter, including the generation of transgenic animals by nuclear transfer.

(B) Responsive to Applicant's alleged arguments that the case law cited by the Examiner is "not relevant," the Examiner rebuts that the case law is in fact relevant to the instant case because it relates to "unpredictable art," which allegedly is the issue at hand.

It is respectfully submitted that Applicant did not argue that the Examiner's case law is "not relevant." Rather, Applicant argued that "unpredictability" alone cannot be considered in a determination of enablement, and that the Examiner had failed to consider the other factors set forth in In re Wands. While unpredictability may provide "reasonable doubt" as to a disclosure being broadly enabling (Ex parte Singh), the inquiry with respect to enablement under 35 U.S.C. §112, first paragraph, is whether it would require *undue experimentation* to make and use the claimed subject matter. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984).

U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE

A consideration of whether or not undue experimentation is required takes into account a number of factors, of which predictability is only one factor. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims.

Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'l 1986).

The case law cited by the Applicant in the previous responses and herein provides the standard for enablement (no undue experimentation) and how to apply and measure that standard. The Examiner, on the other hand, appears to be implying that "predictability of the art" alone need be considered in establishing whether the application is enabling for the methods as claimed. None of the aforementioned cases cited by the Examiner change the standard for assessing enablement, whether the rejection is one of lack of enablement or scope of enablement.

Notwithstanding the above, as discussed herein and previously, Applicant has shown that the methods as claimed herein are not "unpredictable" because (1) the post-filing date art cited by the Examiner in fact demonstrates the promise of nuclear transfer methods and their operability; (2) the disclosure of Wilmut *et al.* is reproducible for the methods of nuclear transfer described and incorporated by reference in the specification and is operative as evidenced by Schnieke *et al.* and issued Patent No. 6,147,276, whose disclosure is identical to that of PCT Application No. PCT/GB96/02099, published as WO 97/07669 and incorporated by reference in the instant application; and (3) the knowledge of those of skill in the art was high as of the application's earliest priority date, as disclosed in the specification and as evidenced by the references of record. Therefore, regardless of whether lack of enablement and/or scope of enablement is alleged on the basis of "unpredictability" alone, or by taking unpredictability

U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE

into consideration with the other factors enumerated in Ex parte Forman, it is respectfully submitted that the Examiner has failed to establish a level of experimentation beyond routine variation that would render the instant methods "unpredictable" to the extent that the standard for enablement is not met.

In addition, the claims as amended in the Amendment after Final filed March 23, 2004, responsive to the Final Office Action specify that the nuclear donor and recipient cells and the host are mammalian. As discussed herein and previously, the teachings of the specification, in light of the advanced knowledge of those of skill in the art of mammalian nuclear transfer and transgenic animal generation as evidenced by numerous publications incorporated by reference in the application and/or provided responsive to the previous Office Action, are adequately enabling for the methods as claimed.

(C) Applicant's alleged argument that the disclosure of Wilmut *et al.* is presumptively enabled because a U.S. patent has issued is deemed unpersuasive because "the issue of enablement of Wilmut was raised based on the questions raised in the state of the art."

It is respectfully submitted that Applicant did not argue that the disclosure of Wilmut *et al.*, nor of the specification which describes the method of Wilmut *et al.* and incorporates it by reference, is presumptively enabled. Rather, Applicant responded to the Examiner's assertion that the method of Wilmut *et al.* has been shown to be irreproducible in other laboratories (*i.e.*, inoperative) by arguing that a U.S. Patent has since issued, with claims to the method of Wilmut *et al.*. This issued patent, whose disclosure is identical to that of PCT publication as WO 97/07669, which is described and incorporated by reference in the instant application, is presumptively valid with an enabling disclosure. Therefore Applicant argued that the instant specification, which describes and incorporates PCT publication WO 97/07669 by reference, is operative because claims that are based on the method of Wilmut *et al.* have issued in U.S. Patent

U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE

No. 6,147,276, whose disclosure, identical to that of WO 97/07669, prescriptively enables the issued claims to the method of Wilmut *et al.*

Moreover, Applicant has responded to the Examiner's assertion regarding the "unpredictability" of the state of the art at the time of filing by providing evidence in the form of numerous references (see above and previously) demonstrating that the knowledge of those of skill in the art of nuclear transfer in mammalian species was high as of the application's earliest priority date, and the methods of nuclear transfer were applicable to a wide variety of mammalian species by variation of parameters that were routine and standard in the art.

(D) Applicant's arguments that the method of Schnieke *et al.* follows the method of Wilmut *et al.* but for very minor modifications are deemed unpersuasive because "applicants do not provide any evidence except for arguments that examiner's enablement analysis was not correct."

First, it is respectfully submitted that Applicant is not required to submit evidence to traverse a rejection on the ground of lack of enablement; "persuasive arguments" will suffice, supported by suitable proof where necessary. (In re Brandstadter, 484 F.2d 1395, 1406-7, 179 USPQ 286, 294 (CCPA 1973)) Applicant respectfully submits that an analysis of the factors set forth in In re Wands, described in detail in previous responses and further discussed herein, leads to the conclusion that it would not require experimentation that is so undue as to render the instant specification not enabling. The Examiner, on the other hand, appears to have applied a single In re Wands factor, "unpredictability," as the standard for asserting a lack of enablement.

Moerover, Applicant disagrees with the assertion that Applicant has provided no evidence. Schnieke *et al.*, which is a reference cited by Applicant, is evidence of the operability of the method of Wilmut *et al.* The Examiner in the Final Office Action alleges that Schnieke *et al.* did not "exactly follow" the method of Wilmut *et al.* because "the source of nuclei were different, the

U.S.S.N. 09/836,911

**HADLACZKY *et al.*
RESPONSE AND RCE**

culture methods were different, *etc.*," and these "improvisations" are allegedly not taught in the specification. Applicant responded to this allegation by pointing to specific citations in Schnieke *et al.* showing that Schieke *et al.* followed the method of Wilmut *et al.* and demonstrated its operability.

Schnieke *et al.* specifically states that nuclear transfer was performed as described in Wilmut *et al.* (see page 2131, caption for Table 1, and col. 3, second full paragraph). Further, the nuclear transfer is from a donor cell that is a fetal fibroblast cell type, which is one of the cell types used in Wilmut *et al.*, and the recipient enucleated oocyte is derived from Scottish Blackface ewes, which is the same source as that used in Wilmut *et al.*. The only difference between Schnieke *et al.* and Wilmut *et al.* is the fetal fibroblast nuclear donor cells in Schnieke *et al.* are derived from Poll Dorset sheep while the fetal fibroblast nuclear donor cells in Wilmut *et al.* are derived from Black Welsh sheep. It is requested that the Examiner point out why this single change Schnieke *et al.* would be considered "not routine."

Variations, if any, between the nuclear transfer methods of Wilmut *et al.* and Schnieke *et al.* are in minor details that are unquestionably routine. Schnieke *et al.* tests the nuclear transfer method of Wilmut *et al.* using a nuclear donor cell that contains a transfected gene - there is no difference in the cell types or steps followed in carrying out nuclear transfer in Schnieke *et al.* compared to the nuclear transfer method taught by Wilmut *et al.* Schnieke *et al.* in fact demonstrates the unquestionable utility of the method of Wilmut *et al.* by demonstrating that the method works when transgenes, such as human Factor IX can be introduced into nuclear donor cells, resulting in live transgenic sheep encoding human Factor IX can be produced by nuclear transfer of the nucleus from the fetal fibroblast into enucleated sheep oocytes (*e.g.*, Table 1 at page 2131).

As discussed above and previously, Applicant also provided evidence in the form of PCT publication WO 02/062131, which demonstrates the *operability*

U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE

of nuclear transfer methods using artificial chromosome-containing nuclear donor cells, and U.S. Patent No. 6,147,276, which has issued claims to the method of Wilmut *et al.* and therefore demonstrates its operability. It is noted that post-filing date references to establish operability of a method are proper. In this instance, although the rejection is under the guise of a lack of enablement, it is asserting that the methods do not work. The disclosures of Wilmut are in the instant application; the issued patent is provided not to establish the enablement of such disclosure but to demonstrate that the Patent Office has determined that the method is operable, since it has issued claims thereto.

On the other hand, Wolf *et al.*, cited by the Examiner as establishing that the method of Wilmut *et al.* has not been reproducible in other laboratories, merely questions the reproducibility of the result in Wilmut *et al.* with respect to a single embodiment, nuclear transfer using an adult nuclear donor cell. Wolf *et al.* that provides no experiments demonstrating that the method of Wilmut *et al.* is not reproducible, nor that the experimentation required to reproduce the method of Wilmut *et al.* would be undue. Wolf *et al.* cites Sgamarella *et al.* (*Science*, 279(51):635-636, (1998); attached hereto) for its assertions regarding the alleged non-reproducibility of the method of Wilmut *et al.*, which, as discussed above, also only speculates without providing any evidence.

Therefore, it is respectfully submitted that responsive to the Examiner's assertion that Schnieke *et al.* carries out several "improvisations" to the method of Wilmut *et al.*, Applicant pointed to evidence in Schnieke *et al.* and other reference showing that (i) these references follow the method of Wilmut *et al.* with insubstantial variations at best; and (ii) Applicant pointed to evidence in the Examiner's reference Wolf *et al.* allegedly demonstrating that the method of Wilmut *et al.* is not reproducible and showed that the reference was speculative as to one embodiment of the method and further provided no demonstration of this or any other embodiment of the method of Wilmut *et al.*.

U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE

Conclusion

In conclusion, it is respectfully submitted that the specification, which describes and incorporates by reference Wilmut *et al.* (1997) Nature 385:810-813, International PCT application Nos. WO 97/07669 and WO 97/07668), teaches and exemplifies the steps of the methods as instantly claimed in which an artificial chromosome is introduced by any suitable method into an appropriate donor cell, such as a mammary gland cell, is then introduced, such as by cell fusion or microinjection, into an unactivated oöcyte, preferably enucleated cell. The specification teaches how nucleation can be effected, how the recipient oöcyte is activated, and how to produce a reconstituted mammalian embryo (claims 23-25, 27-30, 32-39 and 41-56). The specification also teaches introduction of the embryo into a mammalian host. By following the teachings of the specification as provided herein, one of skill in the art can (1) introduce a chromosome into a nuclear donor cell; (2) transfer the nucleus of the nuclear donor cell into an enucleated non-human mammalian recipient cell of the same species; and (3) further transfer the recipient cell into a maternal mammalian host animal for development of a mammalian animal or fetus therefrom. As noted only (1) and (2) are pertinent to claims 23-25, 27-30, 32-39 and 41-56.

This is further evidenced by the references provided by applicant and of record in the application demonstrating success of practicing the nuclear transfer steps of the method as demonstrated by Wilmut *et al.* (1997) Nature 385:810-813, International PCT application Nos. WO 97/07669 and WO 97/07668, incorporated by reference herein. Contrary to the Examiner's assertion that the method of Wilmut *et al.* is not operative, Wilmut *et al.* (and International PCT application Nos. WO 97/07669 and WO 97/07668) demonstrates that by following the steps of the method as provided in the specification, live lambs born after nuclear transfer from a mammary gland cell were produced, thereby rebutting any assertion that the method is inoperable.

U.S.S.N. 09/836,911

**HADLACZKY *et al.*
RESPONSE AND RCE**

Further, a patent application satisfies the requirements of 35 U.S.C. §112, first paragraph, as long as it provides sufficient disclosure, either through illustrative examples or terminology, to teach those of skill how to make and use the claimed subject matter with reasonable, but not undue, experimentation. The instant application enables one of skill in the art to, by following the methods set forth therein, generate artificial chromosomes, readily identify the resulting artificial chromosomes based on the detailed characterization provided in the specification, incorporate foreign nucleic acid, *e.g.*, heterologous DNA encoding a product, into an artificial chromosome, and isolate and transfer artificial chromosomes into cells for use in a variety of applications including the generation of transgenic animals by nuclear transfer and other such methods. By virtue of Applicant's provision of these artificial chromosomes and the teachings of the specification, those of skill in the art are able, without undue experimentation, to make and use the artificial chromosomes and to combine the artificial chromosomes with known recombinant DNA procedures, many of which are referenced in the specification, to achieve any number of particular outcomes, including the introduction and stable maintenance of artificial chromosomes in cells, such as nuclear donor cells (claims 23-25, 27-30, 32-39 and 41-56) and also production of transgenic animals by nuclear transfer and other such methods (claims 26, 31, 40 and 57-60).

Applicant respectfully maintains that a consideration of the factors enumerated in Ex parte Forman leads to the conclusion that undue experimentation would not be required to introduce an artificial chromosome into a nuclear donor cell and transfer the nucleus of the nuclear donor cell into an enucleated recipient cell (claims 23-25, 27-30, 32-39 and 41-56); nor is it required to further permit the recipient cell to develop into an animal or fetus in a host (claims 26, 31, 40 and 57-60). The application teaches methods for introduction of satellite artificial chromosomes into cells that is not limited by the species of satellite artificial chromosome or species of cell. The application

**U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE**

further teaches nuclear transfer of the nuclear donor cell nucleus into an enucleated recipient cell. The application teaches methods for introduction of the resulting recipient cell into an animal and production of transgenic animals. Therefore, Applicant respectfully maintains that the instant application teaches how to make and use methods that are commensurate in scope with the instant claims.

In light of the breadth of the claims, the extensive teachings and examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in the art, the fact that it is predictable that artificial chromosomes can be introduced into cells (claims 23-25, 27-30, 32-39 and 41-56) and can be further used to generate transgenic animals (26, 31, 40 and 57-60), it would not require undue experimentation for one of skill in the art to practice the claimed methods.

Accordingly, a consideration of the factors enumerated in Ex parte Forman leads to the conclusion that undue experimentation would not be required to introduce an artificial chromosome into a nuclear donor cell, transfer the nucleus of the nuclear donor cell into an enucleated recipient cell. Therefore claims 23-25, 27-30, 32-39 and 41-56 are enabled. Similarly, with respect to claims 26, 31, 40 and 57-60, it would not require undue experimentation to introduce the enucleated recipient cell or an embryo derived therefrom into a host in which it develops into a fetus or animal in the host.

Policy Considerations

In addition to the above, it is clear that Applicant's discovery, particularly of SATACs is of a pioneering nature, and, as such, is entitled to broad claim protection. As taught in the above-captioned application, any methods known in the art pertaining to introduction of foreign genes carried in traditional, standard sources (such as genes harbored in expression vectors) into cells for any variety of purposes, e.g., gene therapy, protein production and the generation of transgenic animals, including nuclear transfer methods, can be

U.S.S.N. 09/836,911

HADLACZKY *et al.*
RESPONSE AND RCE

applied in similar fashion to the introduction of artificial chromosomes, particularly SATACs, into cells. The application describes and demonstrates that once the artificial chromosomes are generated and isolated and/or introduced into cells, then any known procedure that has previously been performed with any heterologous gene from any source is applicable to the SATACs (as well as the minichromosomes) carrying foreign genes of interest. The application is replete with descriptions of numerous uses of SATACs as well as the minichromosomes.

It therefore is respectfully submitted that the claims directed to methods of nuclear transfer and, further, producing transgenic animals using SATACs are commensurate in scope with the discovery and its disclosure within the above-captioned application. It would be unfair and contrary to the Constitutional mandate set forth in Article, Section 8, to deprive Applicant of protection of the broad applications of the pioneering discovery disclosed and described in the subject application.

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**U.S.S.N. 09/836,911
HADLACZKY *et al.*
RESPONSE AND RCE**

In view of the above remarks, and the amendments and remarks responsive to the Final Office Action, entry of which respectfully is requested herein, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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